## REMARKS

In this communication, Claims 7, 17, 26, 30, 32, 34, 35, 36 and 39 were amended. Amendments to Claims 7, 26, 30, 32, 34, 35, 36 and 39 were made to improve the readability and consistency of language of those claims without changing their meaning. The amendment to Claim 17 corrects errors in that claim based on incorrect copying of information provided in and supported by paragraph [0049] of the specification. No claims were cancelled or added. Claims 8, 9, 11-15, 31-35, and 39 were previously withdrawn from examination. As such, Claims 7, 10, 16-30, 36-38, and 40 are currently under examination. The Examiner's rejections are as follows:

I) Claims 7, 10, 16-24, 26, 28, 30, 36, 38, and 40 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Soares et al. (U.S. Pat. 5,830,662) and Lorincz et al. (U.S. Pat. 6,136,535); and

II) Claims 25, 27, 29, and 37 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Soares et al. and Lorincz et al. as applied to Claims 25 and 36, and further in view of Hall et al. (U.S. Pat. 5,994,069).

### I. Obviousness Rejection Over Soares et al. and Lorincz et al.

The Examiner rejected Claims 7, 10, 16-24, 26, 28, 30, 36, 38, and 40 under 35 U.S.C. 103(a) as allegedly unpatentable over Soares et al. (U.S. Pat. 5,830,662) and Lorincz et al. (U.S. Pat. 6,136,535) (Office Action, page 2). Applicants respectfully disagree with this rejection and submit that no *prima facie* case of obviousness has been established.

The Examiner has relied specifically on Figures 1A and 4 of Lorincz to maintain this rejection. The lack of teaching in these figures is specifically further rebutted below. First, however, Applicants provide herewith a Declaration of Dr. Gary Dahl refuting the asserted obviousness.

#### A. Declaration of Dr. Gary Dahl

Included with this Response is a Declaration by Dr. Gary Dahl as one of skill in the art with many years of experience in the area of RNA transcription. As explained in the Declaration, when the terms in the claims are properly considered, the prior art does not teach or suggest the claimed invention. For example, as explained by Dr. Dahl, the prior art does not provide

methods wherein: 1) a sense promoter primer is used, or 2) wherein a sense promoter primer is used to generate RNA products from one or multiple target nucleic acids in a sample. As explained in the Declaration, a sense promoter primer or its use is not taught in the prior art. As such, Applicants submit that all of the presently pending claims should be allowed.

Applicants respectfully submit that the Dahl Declaration helps to put the present claims in the proper context of transcription-related art, and explain why the technical arguments regarding Figures 1A and 4 of Lorincz fail to demonstrate any relevant prior art, as also further specifically described below. As such, Applicants request that that the rejections be withdrawn.

**B. Figure 1A of Lorincz**

In the current Office Action, the Examiner cites Figure 1A of Lorincz stating:

> "[t]his is also shown in Figure 1A as presented in the prior Office Action and which teaching Applicant does not rebut." (Office Action, page 3).

Applicants respectfully note that Figure 1A of Lorincz et al. has been specifically rebutted by Applicants in both an Office Action Response (dated April 30, 2008) and an interview (dated May 8, 2008). However, in addition to referring the Examiner to the Declaration of Dr. Dahl, the Applicants wish to repeat and add to the prior rebuttal below in order to more clearly explain why Lorincz et al. does not teach against the presently claimed invention.

As part of the rejection, the Examiner asserts that Lorincz et al. teaches the formation of a circular substrate and cites a paragraph from columns 5 and 6 of Lorincz et al. as allegedly providing an anticipatory teaching. However, in order for this to be relevant to the present claims, the circular substrate taught by Lorincz et al. must comprise a covalently-closed circle which comprises the sense promoter sequence derived from a sense promoter primer as defined in the present application. As such, the sense promoter primer must exhibit a sense promoter sequence in its 5'-portion and a target-complementary sequence in its 3'-portion. This criterion does not hold. None of the promoter primers of Lorincz et al. exhibit a sense promoter sequence in its 5'-portion; the promoter sequences in the oligonucleotides of Lorincz et al. exhibit anti-sense promoter sequences. This is illustrated by the sequences of the three promoter primers or

oligonucleotides given in the Examples of Lorincz , which are copied below with the anti-sense promoter sequences underlined:

SEQ ID NO: 1 (from EXAMPLE 1 under columns 17 and 18):

5'AGTAAAGCCAGAGGAGATCTTAATACGACTCACTATAGGGAATTCCTGCAG AATGGGATAGATTG-3'

SEQ ID NO: 2 (from EXAMPLE 5 at bottom of column 22):

5'-P-CTCCCCGTCTGTGCCTTCTCATCTGTAATACGACTCACTATAGGGAAT TCCAGAGTCTAGACTCGTGGTGGAC-S-T-S-T-3'

SEQ ID NO: 3 (from EXAMPLE 5 at bottom of column 22):

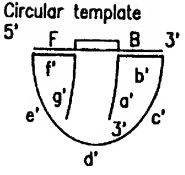
5'-P-CTCCCCGTCTGTGCCTTCTCATCTGTAATACGACTCACTATAGGGAAT TCATCGCCGCGTCGCAGAAGATCTC-S-A-S-A-3'

As discussed by Dr. Dahl in the Declaration, it is also important for the method of the pending claims that the the sense promoter-containing first-strand cDNA is ligated to form a covalently-closed circle, since this is the step of the method that operably joins the sense promoter sequence to the DNA polymerase extension product. Thus, in order to determine if Lorincz provides a teaching that is relevant to the present method, one must look at the type of "circle" being taught by Lorincz et al. The quotation is reproduced below, with the sentences omitted by the Examiner in his response added back in (shown in bold):

> In one preferred embodiment, a nucleic acid and a promoter-primer are hybridized. **The primer portion of the promoter-primer is designed to be complementary to non-contiguous portions of the target region. For example portions at both ends of the target region of the nucleic acid may be selected for hybridization. In addition, the promoter-primer is designed to contain a promoter sequence for an RNA polymerase.** Upon hybridization, the primer portions of the promoter-primer link the 5' and 3' end portions of the target region of nucleic acid, such that the promoter sequence portion is sandwiched between the two hybridized end sequences. The result of this hybridization is the formation of a circle.

Applicants submit that the omitted portions of the above quote shown in bold are important in order to understand what is being taught in this paragraph. In particular, the primer portion of the promoter-primer of Lorincz et al. is designed to be complementary to **non-contiguous** portions

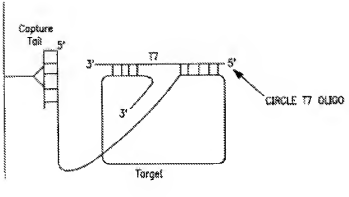
of the target region. Such a configuration results in the so-called "circle" referred to at the end of this paragraph and indicates that a circular nucleic acid as currently claimed is not being taught. Instead, what is taught is a circular configuration formed by two different linear polynucleotides, including an unconnected "top" promoter-primer and a "bottom" target nucleic acid, which when annealed together form the so-called "circle" contemplated by Lorincz et al. Figure 1A of the Lorinz et al. reference provides a visual depiction of the so-called "circle." This configuration results in what the cited paragraph calls a "circle" and what the figure calls a "circular template." However, as can be seen below in Figure 1A from Lorincz, no actual continuous circle is generated as recited in the present claims, wherein the ends of the cDNA product are ligated together to form a circle that contains the promoter-primer.




Thus, this is obviously not the same as the covalently-closed circle described in the present application, the formation of which covalently-closed circle is important and essential for the method of the presently considered claims. Therefore, this rejection should be withdrawn.

### C. Figure 4 of Lorincz

In the current Office Action, the Examiner also cited Figure 4, below.



Applicants previously rebutted the Examiner's arguments related to this figure as well, and it is further rebutted in the present Declaration of Dr. Dahl. This rebuttal can be briefly summarized as follows:

The "circle T7 oligo" in Figure 4 of Lorincz is an anti-sense promoter oligonucleotide that exhibits an anti-sense promoter sequence, not a sense promoter primer that exhibits a sense promoter sequence as defined in the present specification. Still further, the method of Lorincz, of which an initial step showing how the circle T7 oligo is captured and binds is shown in the figure, does not comprise the steps of extending a sense promoter primer with a DNA polymerase or ligating the sense promoter-containing first-strand cDNA to itself to form a covalently-closed circle, and also it does not show annealing of an anti-sense promoter oligonucleotide to the sense promoter sequence. Thus, Lorincz et al. does not teach or suggest *any* of the steps of the presently-claimed method.

Soares et al. used a ligase to clone a sequence into a dual promoter vector. Such vectors are not sense promoter primers or even primers as defined in the present application, and it was not used as such by Soares et al. Therefore, Soares is not relevant to the present invention.

In light of the above, it is clear that the combined teaching of Soares et al. and Lorincz et al. do not teach the important aspects of the methods in the present claims. As such, Applicants submit that no *prima facie* case of obviousness has been established and the present rejection should be withdrawn.

**II. Obviousness Rejection Over Soares et al., Lorincz et al., and Hall et al.**

The Examiner rejected Claims 25, 27, 29, and 37 under 35 U.S.C. 103(a) as allegedly unpatentable over Soares et al. and Lorincz et al. as applied to Claims 25 and 36, and further in view of Hall et al. (U.S. Pat. 5,994,069) (Office Action, page 4). Applicants respectfully submit that this rejection fails for the same reasons outlined above. The present application teaches how to use a sense promoter primer. None of the cited references has taught the use of a sense promoter primer, or the steps of the method of the present claims, either alone or in combination. As such, Applicants respectfully submit that this rejection should be withdrawn and the claims allowed.

## CONCLUSION

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned at 608-662-1277.

Dated: December 21, 2009

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